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(54) Title: ARTIFICIAL TEARS

(57) Abstract

An artificial tear composition for use in treating or preventing dry eye syndrome, or sore eyes, containing a phospholipid, and optionally hyaluronic acid or its salts, in a suitable carrier. The carrier is preferably an isotonic salt solution such as saline, or else propylene glycol. A method of treating sore eyes or dry eye syndrome using the composition as described. The method can be used to treat eyes wearing contact lenses.

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ARTIFICIAL TEARS

TECHNICAL FIELD

The present invention relates to an artificial tear composition and in particular to artificial tear compositions which contain phospholipids, and optionally hyaluronic acid or a salt thereof.

BACKGROUND ART

Artificial tears are currently available as eye drops and offer limited relief to dry eye syndrome. Such prior art formulations sometimes include hyaluronic acid, as this is a major component of natural tears.

It is an object of the present invention to provide an improved artificial tear solution which will substantially overcome, or ameliorate the abovementioned disadvantage of offering little relief to eyes to combat dry eye syndrome and also as treatment of sore eyes and other dry eye conditions.

Therefore, there is a need for an artificial tear composition which ideally would have one or more of the following properties: excellent lubrication to allow effortless sliding of the eyelid over the ocular surface or a contact lens; the capability to provide excellent of lubrication under high load bearing conditions relevant to an ill fitting contact lens and the pressure of high spot as the eye turns; reduction of fluid evaporation to maintain the tear film; reduction of the disjoining pressure tending to rupture the tear films and expose dry spots in the ocular surface; provision of a non-stick surface preventing adhesion of the ocular surface to a contact lens or eyelid; or provision of a biological barrier to invasion of the eye by impinging air-borne pathogens such as bacteria or viruses.

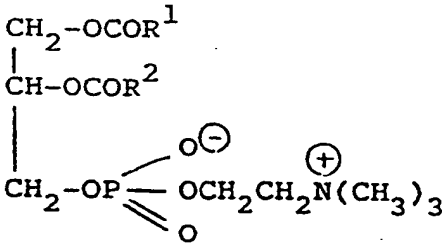
It is known from PCT/AU88/00322 that a lubricant composition comprising at least one surface active phospholipid, hyaluronic acid or a water soluble salt thereof in saline solution, is effective in the treatment of arthritis, osteoarthritis and rheumatic diseases by improving lubrication of surfaces in particular surfaces in the joints of animals and

humans, and acting as a lubricant between tissue surfaces in contact with each other. As disclosed in PCT/AU88/000322, certain phospholipids, especially the disaturated phosphotidylcholines (lecithins), can give coefficients of kinetic friction of less than 0.01 and as low as 0.002. It was also found that these lower coefficients of friction could be obtained for loads as high as 13 $Kgcm^{-2}$.

Hyaluronic acid is a naturally occurring, high viscosity mucopolysaccharide having alternating ß 1-3 glucuronidic and ß 1-4 glucosaminindic bonds. Hyaluronic acid has a molecular weight within a range of 50,000 to 8,000,000 depending on the source, methods of preparation and determination. It is well known that hyaluronic acid and its salts, can be obtained from animal tissue and some bacteria, e.g. umbilical cords, vitrious humour, synovial fluid, rooster combs, pathological joints, groups A and C hymolitic streptococci and in skin, as well as from synthetic sources.

Phosphatidylcholine, commonly known as lecithin, is a phosphatide found in all living organisms (plants and animals). It is a constituent of biological membranes and is involved in permeability, oxidative phosphorylation, phagocytosis, and chemical and electrical excitation. Lecithin has been identified in many animal tissues and organs such as in the brain, nervous system, liver, heart, lungs, kidneys, blood, milk, sperm, in micro-organisms and throughout the vegetable kingdom.

Lecithin is a mixture of the diglycerides of stearic, paermitic and oleic acids linked to the choline ester of phosphoric acid and can be represented by the general formula I



(I)

where R^1 and R^2 and fatty acid residues. Usually one acid is saturated and the other unsaturated.

It has now surprisingly been found that a solution or suspension comprising a surface active phospholipid, which optionally also contains hyaluronic acid (HA) or its salt, in an opthalmically suitable carrier of diluent, can treat and lubricate dry eyes and other conditions, as well as treating sore eyes. Other opthalmic applications include a lubricant for intra-ocular lenses and for post-cataract surgery, as well as in the new eye cosmetics.

A further use is in the treatment of conjunctivitis and similar conditions. The addition of phospholipid to medicinal formulation for treating conjunctivitis assists in reducing the intense pain, especially when moving the eyelid relative to the eye, by providing lubrication and release action.

DISCLOSURE OF INVENTION

One aspect of the present invention concerns an artificial tear solution consisting of a suspension or solution of a phospholipid in an opthalmically suitable carrier or diluent.

Also disclosed is a method of treating/lubricating dry eyes, which comprises applying to an eye an artificial tear solution consisting of a suspension or solution of a phospholipid in an opthalmically suitable carrier or diluent.

Preferably the composition or treatment also includes hyaluronic acid, or a physiologically suitable salt thereof.

Another aspect of the invention is when the solution is used as a lubricant between the eyelid and the ocular surface or a contact lens.

Some phospholipid suspensions are viscous particularly those containing hyaluronic acid or its salts, but in the case of artificial tear formulations in accordance with the invention, the viscosity of the resultant formulation can be controlled, if necessary, by the concentration of the phospholipid solution, and if hyaluronic acid is present, by selection of hyaluronic acid of the appropriate molecular weight. The artificial tear solution is diluted to a suitable viscosity, with an opthalmically suitable carrier or diluent for

application to the eye.

Some of the phospholipids useful in the present invention are listed in the following table.

TABLE 1

Phosphoglycerides

phosphatidic acids
cytidylic phosphoglycerides (CDP diglyceride)
choline phosphoglycerides (CDP diglyceride)
choline phosphoglycerides
ethanolamine phosphoglycerides
N-methylethanolamine phosphoglycerides
N,N-dimethylethanolamine phosphoglycerides
N-acylethanolamine phosphoglyceride
serine phosphoglycerides
N-2-(hydroxyethyl)alanine phosphoglyceride
glycerol phosphoglycerides
glycerophosphate phosphoglyceridesphosphatidylglycerol
phosphoglyceride (diphosphatidylglycerol)
mono and diacylglycerol phosphoglycerides (lysobisphosphatidic acids)
glucosaminylglycerol phosphoglyceride
O-amino acid esters of glycerol phosphoglycerides
inositol phosphoglyceride
inositol monophosphate phosphoglyceride
inositol diphosphate phosphoglyceride
monomannosyl-hexamannosyl inositol phosphoglycerides
glucose phosphoglyceride
O-diglucosylglycerol phosphoglyceride

Phosphoglycolipids

diacyl (glycerylphosphoryldiglucosyl) glycerol

Phosphodiol lipids

acyl dihydroxyacetone phosphate
alkyl dihydroxyacetone phosphate

Phosphosphingolipids
spingomyelin (ceramide phosphorylcholine)
ceramide phosphorylethanolamine
ceramide phosphorylglycerophosphate
ceramide phosphorylinositol-containing lipids

Preferably the phosphatidylcholine is suspended in solution by ultrasonic dispersion, if this is required.

The opthalmically suitable carrier or diluents useful in the present invention are substantially isotonic. Substantially isotonic solutions are defined for present purposes as containing 270-310 milliosmoles/kg of solutes. The tonicity adjusting agent is employed to bring the final solution tonicity within the stated ranges if not already there due to contributions of the other ingredients.

The preferred isotonicity adjusting agents are ionic salts, e.g. NaCl.

Otherwise a solvent such as propylene glycol can be used to dissolve the phospholipid and other ingredients. Alternatively, chemically similar compounds to propylene glycol may be used, but such compounds should be suitable for opthalmic use.

A combination of propylene glycol or similar diluent together with water or saline solution may also be used.

If propylene glycol alone is used as the carrier, then the phospholipid may be present in an amount of about 20-200 mg/ml. The amounts of the other ingredients can be adjusted accordingly, in accordance with opthalmic formulations known to be suitable for eye application.

Optional ingredients such as preservatives, buffers, surfactants, lubricants pharmaceutically active compounds and vasoconstricting (i.e. decongesting) agents may also be included in the solutions of this invention.

Preservatives useful in the present invention should not cause irritation to the eye. Strong binding of the preservative to contact lens is also undesirable since it causes the preservative to accumulate in the eye.

Preservatives preferred for use in the present solutions are any effective, non-irritating preservative which is

compatible with hydrogels. Some suitable preservatives include sorbic aid and EDTA.

Any biostatic amount of preservative which prevents contamination of the solutions may be used.

The surfactants useful in the present invention are non-irritating to the eye and are, preferably, non-ionic. The pharmaceutically active compounds useful in the solutions of this invention are those which have a prophylactic or therapeutic effect on eye disorders. Some examples of pharmaceutically active compounds include, for example, compounds for the treatment of glaucoma, conjunctivitis, compounds for the treatment of red eyes and compounds for inflammatory ocular conditions.

The artificial tear solution of the present invention can impart excellent lubrication at low load which can, by conventional theory, be attributed to the fluid film of hyaluronic acid solution. At points of high load where fluid will be squeezed out from between the surfaces sliding at such low velocities, there is excellent boundary lubrication provided by an oligolamellar layer of phospholipid. This solid lubrication is envisaged as being imparted in much the same way that colloidal graphite functions when added to gear oil, that is providing a layer directly attached to the sliding surface and its counterface. It has been known for some time that a layer of phospholipid is directly attached to the ocular surface but no significance has hitherto been attribued to that finding.

To summarise its lubricating properties, the product can reduce the coefficient of friction to value between 0.02 to 0.006, and occasionally as low as 0.0007. The major advantage of this product is at such very low friction was achieved at low velocities under high load (18 Kg/sq.cms).

The present artificial tear solution also has release properties, Lecithins are widely used as release agents, that is for the adhesive or antistick properties. This should also apply to the ocular surface, preventing sticking of a contact lens or the eyelid. Tests have shown that the force of adhesion by protein may be reduced by as much as 99%, in some situations.

The artificial tear solution of the present invention enhances the retention of fluid by the tear film in at least two

ways. Firstly, it is well known that hyaluronic acid tends to retain water in loose association with its long hydrophilic molecules. Secondly, phospholipids might provide a monolayer reducing evaporation at the air-aqueous interface in much the same way that the industrial surfactants have been on dams to cut water evaporation.

The artificial tear solution of the present invention also reduces film rupture. A water layer place on top of a hydrophobic surface has a high disjoining pressure tending to rupture the layer exposed to dry surface. This phenomenon is witnessed in siphoning water out of a Teflon-lined frying pan. When the depth of the water is reduced to about 1 to 1.5 millimetres, the layer ruptures spontaneously to expose dry surface is also hydrophobic and, therefore it will tend to rupture the tear film unless we blink every twenty seconds or so. Our tests have demonstrated a contact angle of about 70° on the ocular surface of bull's eyes by comparison with values of 108° for teflon and 0° for wettable surfaces. The contact angle is the angle between the solid surface and the tangent to the air aqueous interface at the triple point where all three phases meet.

The disjoining pressure, and hence, the tendency for the film to rupture can be reduced if the surface energies of both the tissue-liquid and air-liquid interfaces are reduced. The latter can be reduced by hyaluronic acid acting as a wetting acid, while the former can be reduced by locating a surfactant monolayer on the surface of the tear film to reduce surface tension. This could be achieved by the same monolayer reducing surface evaporation.

MODES FOR CARRYING OUT THE INVENTION

The invention is now described with reference to examples.

EXAMPLE 1

A determination was made of the lubricating effect of a phospholipid formulation on an eye. A phospholipid formulation was prepared by suspending 3mg/ml of DPL (phophatidyl choline)

with 10mg/ml of hyaluronic acid by means of ultrasonic dispersion.

10 eyes from five freshly killed sheep were tested on a friction machine, and gave coefficients of kinetic friction (μ) ranging from 0.01 to 0.04. The same eyes were then rinsed for 10 minutes in a solvent (2:1 chloroform: methanol) to remove the natural phospholipid present, and tested again. The friction was much increased and, in fact, was off the scale of the transducer, which corresponds to $\mu > 0.1$. When the phospholipid lubricant formulation was then applied to the eyes and the coefficients of kinetic friction determined again, μ was in the range of 0.01 to 0.04.

EXAMPLE II

Another test was mode of the lubricating ability, namely wear, of the same phospholipid formulation used in Example I. A 4-ball test was performed by clamping together three ball bearings so that they cannot move and then applying a fourth so as to make three points of contact with the others. A shaft welded to the fourth ball bearing is rotated at 1,500rpm under a load of 40kg for one hour and the depths ofd the resulting grooves in the three fixed ball bearings measured by a mocroscope, and averaged. The groove averaged 0.70mm, with the use of the phospholipid formulation of Example I. When the test was repeated with another phospholipid formulation, but this time increasing the phospholipid concentration to 4mg/ml, with the hyaluronic acid remaining at 10mg/ml, the value for the average depth of the resulting grooves was 0.69mm.

These results demonstrate the effectiveness of phospholipids as lubricants. The test results using phospholipids compare favourably with such values as 1.4mm for milk, 0.35mm for the very best lubricating oils, and 0.7 to 0.9mm for typical commercial aqueous lubricants.

EXAMPLE III

A formulation of a lecithin dissolved in propylene glycol was prepared, and found to have similar advantageous results to

those of Example I. A composition of lecithin and hyaluronic acid dissolved in propylene glycol also produced successful results.

THE CLAIMS

1. An artificial tear composition, for the prophylaxis or treatment of dry eye syndrome and other conditions that cause sore or dry eyes, which comprises a suspension or solution of a phospholipid, and optionally hyaluronic acid or a physiologically suitable salt thereof, in an ophthalmically suitable carrier.

2. The artificial tear composition of claim 1 wherein the carrier is saline solution.

3. The artificial tear composition of claim 1 wherein said carrier is propylene glycol.

4. The artifical tear composition of claim 1 which contains hyaluronic acid or a physiologically suitable salt thereof, selected so as to optimize the viscosity of the composition.

5. The artificial tear solution of claim 1 which also contains any one or more of preservatives, buffers, surfactants, lubricants, phamaceutically active compounds or vasoconstricting agents, suitable for opthalmic use.

6. A method for the prophylaxis or treatment of dry eye syndrome or other conditions that cause dry or sore eyes, which comprises applying to an eye an artificial tear composition of a phospholipid, and optionally hyaluronic acid or a physiologically acceptable salt thereof, in an opthalmically suitable carrier.

7. The method of claim 6 wherein the carrier is saline solution.

8. The method of claim 6 wherein the carrier is propylene glycol.

9. The method of claim 6 wherein the eye has a contact lens thereon.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 91/00063

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5] A61K 31/685. 31/66. 31/70. 31/725

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	A61K 31/68, 31/66, 31/70, 37/22

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

AU : IPC as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, [11] with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	US,A, 4421748 (TRAGER et al) 20 December 1983 (20.12.83) See Columns 3 and 4	(1,2,5-7)
X	EP,A1, 0312814 (OCULAR RESEARCH OF BOSTON INC) 26 April 1989 (26.04.89) See example 1	(1,2,5-7)
X	US,A, 4804539 (GUO et al) 14 February 1989 (14.02.89) See the claims and abstract	(1,5,6)
P, X	WO,A, 90/11781 (ALCON LABORATORIES, INC) 18 October 1990 (18.10.90) See claims 1 and 2 and the examples	(1,2,5)
X	US,A, 4839175 (GUO et al) 13 June 1989 (13.06.89) See claims 1 and 8 and the abstract	(1,5,6)

(continued)

* Special categories of cited documents: 10

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5 June 1991 (05.06.91)	12 June 1991
International Searching Authority	**Signature of Authorized Officer**
Australian Patent Office	S. CHEW

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	AU,A, 27553/84 (REIFENRATH, Rainer) 8 November 1984 (08.11.84) See claims 1,5,21 and 22	(1,2,5)

V. [ ] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[ ] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2.[ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[ ] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1.[ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.[ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 91/00063

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members					
EP 312814	US	4914088	JP	1146824		
US 4804539	EP	316345	WO	8800824	US	4839175
US 4839175	EP	316345	WO	8800824	US	4804539
WO 9011781	AU	54297/90	CA	2013770	ZA	9002593
AU 27553/84	DE	3316012	EP	100964	IL	71712
	JP	59044326	ZA	8403254	DE	3228629

END OF ANNEX